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Original Research Paper

A simplified approach to determine effective surface area and porosity of low bulk density active pharmaceutical ingredients in early development

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ABSTRACT

It can be difficult to accurately measure true density of low bulk density materials, which are frequently used in drug products. This was demonstrated on a crystalline model API. Uncertainty was related to insufficient sample volume. The error function was theoretically described by assuming an inverse relation to the sample volume. Hence, an easy to implement guideline to increase accuracy was established. Verification was performed using spray dried dispersions, SDDs. Practically, bulk density rather than sample volume was used for risk evaluation. Procedures such as compacting a sample into a pellet or using a low volume instrumental calibration mode were implemented. Risk assessment of morphology or crystal form change was included in the guideline.

Furthermore, a simplified approach using true density as a central parameter was developed to assess surface area and porosity. For spherically shaped SDDs, surface area can be estimated from true density and particle size, and porosity can be estimated from true and bulk densities. A surface roughness parameter, theoretically derived, leads to a surface area scale factor of 2.28, which provides results in good agreement with the experimentally obtained surface areas. Also, SDD porosities follow a trend similar to those obtained by mercury porosimetry.

1. Introduction

Often, active pharmaceutical ingredients (APIs) exhibit low bulk densities which make them difficult to handle for development of robust manufacturing processes. In API manufacturing, low bulk density materials reduce batch size and product throughput, while increasing turnaround time and storage space, and therefore, the cost of the final drug product. Also, these APIs often exhibit poor flow, compactibility [1], and other issues that need to be addressed during development.

It was estimated that 40–70% of new APIs are poorly water soluble which subsequently results in low oral bioavailability [2]. One viable approach to enhance dissolution and bioavailability of poorly soluble APIs is to stabilize the amorphous API, through the use of spray drying. This produces an amorphous API in a polymer matrix, described as a spray dried dispersion (SDD). Along with the many naturally occurring low bulk density APIs, SDDs also generally exhibit low bulk density [3]. Hence, it could be predicted that low bulk density APIs will become more dominant in the pharmaceutical industry. However, to our knowledge, accurate and efficient solid-state characterization approaches to determine true density, surface area and porosity of low bulk density APIs and SDDs have not been fully investigated.

True density (solid mass divided by true solid state volume without voidage of open and closed pores (if present) and internal and interparticle voids (if present)) is frequently required to assess formulation ingredients and processes [4]. It is a fundamental material property that is useful in the evaluation of powder and tablet porosity [5–9], particle mechanical properties [10], powder fluidization [4], and suspension settling [4], all of which impact the formulation development of oral solid dosage forms [4]. As one example, true density is required to predict compressibility

Abbreviations: ANOVA, analysis of variance; API, active pharmaceutical ingredient; IGC, inverse gas chromatography; HPMC, hydroxypropyl methylcellulose; SSA, specific surface area; SDD, spray dried dispersion.

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properties of pharmaceutical materials by modeling the density–pressure profiles during tabletting [10,11]. Inaccuracy of the true density is a significant source of error that can lead to misleading results [11]. Unfortunately, the possible impact of true density measurements on solid-state characterization techniques has not been studied in detail.

True density can be predicted [12,13] or calculated based on the crystal structure if crystalline material is available [4,9]. Experimentally, true density is commonly measured using helium pycnometry, which gives the closest approximation to the true solid state density [14]. Most water-containing powders, e.g., solvates, hydrates, amorphous drugs, some excipients, and tablet formulations, can release water in a dry helium atmosphere [5]. Released volatile components cause significant errors to the true density measurement by overestimating the real density values [8,9]. Additionally, the morphology and crystal form of most water-containing solids could be altered during drying [6] resulting in a higher magnitude of error. Previously it was reported [15] that insufficient sample size leads to underestimation of the true density value. Tamari et al. [16–18] reported that insufficient filling factors, which is the ratio of true solid state volume to sample chamber volume, is one of the main sources of uncertainty in the true density measurement. The work reported herein evaluates these issues in two interconnected parts: (i) the evaluation of the impact of low bulk density materials on the true density measurements, which exhibit much lower filling factors than previously studied [17] and (ii) the development of a simplified approach to access surface area and porosity, by only relying on particle size, and true and bulk densities.

To investigate the effect of insufficient sample volume, a crystalline model API was chosen which has no limitations such as loosely bound water and/or solvents. Additionally, using a well characterized crystalline material provides a theoretical reference value for judging accuracy of experimental true density values. Also, two different SDDs with relatively low and high bulk densities, were chosen to investigate the effect of insufficient sample volume. Samples were treated as unaltered, tapped, hand pressed, and compacted as a pellet to study the impact of sampling on the true density values. This resulted in guidelines that permit accurate measurement of the true density of low bulk density materials.

This guideline enables highly accurate measurement of true density values, which are required to develop the simplified approach to assess surface area and porosity. The standard techniques to determine the specific surface area (SSA) are volumetric nitrogen adsorption at 77 K [19] and inverse gas chromatography (IGC) at ambient temperature [20–22]. Because SDDs exhibit a low surface area, standard volumetric nitrogen adsorption is not suitable for these pharmaceutical materials [23]. Krypton adsorption at 77 K is suitable for low surface area materials [23], but there is still the potential risk of a structural form change of pharmaceutical materials either during sample conditioning or measurement at higher or lower temperatures. Krypton adsorption could be employed for these SDDs if a lower temperature were applied to flow outgassing [24]. Alternatively, IGC is suitable for assessing low surface area materials [25].

In this work, a simplified approach was employed to calculate the geometric surface area from the true density and particle size. The advantage to using this simplified approach is that it is less time consuming, more cost efficient and easier to operate in a manufacturing environment. Furthermore, the simplified approach calculates porosity from the true and bulk densities. This concept has been employed to determine porosities of food [26], grains [27], meteorites [28] and soils [29–32]. Additionally, porosities used for acoustical modeling have been determined for porous materials by air-based systems, which are limited by comparing air volumes of air-saturated solids at ambient pressure [33–35]. To evaluate the suitability of the simplified approach, the powder properties of a series of SDDs derived from different spray drying processes that varied SDD particle size were compared. Indeed, true density is a central factor in developing a simplified approach to assess surface area and porosity, and therefore, requires high accuracy, especially for low bulk density materials.

2. Materials and methods

The material used during this study was a spray dried amorphous dispersion consisting typically of 25% API of a developmental drug and 75% polymer (HPMCAS-LG or MG, with low and medium granular grade); exact polymer ratios are listed in Table 2. The API was dissolved in acetone for spray drying. Three different spray dryers were used: Micro (lab scale), PSD-1 (I) (pilot plant scale), and PSD-2 (II) (plant scale). The spray drying process parameters (nozzle, temperature, pressure, etc.) of PSD-1 and PSD-2 were altered to make consistent materials. However, it could be assumed that the different average porosities of the materials from the different spray dryers may be related to the scale of the process.

2.1. Differential scanning calorimetry

Differential Scanning Calorimetry experiments [36,37] were performed using a TA Instrument (Q2000 Modulated DSC, TA Instruments, New Castle, DE, USA). Sample weight was between 4 and 8 mg. Analysis of the results was carried out by TA Universal Analysis software. The glass transition temperatures of representative SDDs were 78.7 °C (high bulk density SDD) and 90.7 °C (low bulk density SDD), determined by the modulated version (2.5 °C min^{-1} heating rate, 1.5 °C amplitude, 60 s modulation, 0–200 °C). The crystalline API had a melting point of 159.8 °C when determined by a conventional version (10 °C min^{-1} heating rate, 25–300 °C).

2.2. Gas displacement pycnometry

Densities of the crystalline API and SDDs were measured using a Micro-Ultrapycnometer 1200e (Quantachrome Instruments, Boynton Beach, FL, USA). The pycnometer was operated with the 4.5 cm^3 modulus (using a 4.5 cm^3 sample chamber volume). The measurements were conducted under ambient temperature and humidity with a target pressure of 19 psi. The equilibrium rate was in auto mode. The pycnometer was calibrated with certified stainless steel calibration spheres on the day of use. Two calibration modes were used: (i) a low volume calibration mode that uses a single stainless steel calibration sphere with a certified volume of 1.0725 ± 0.0004 cm^3, (ii) a standard calibration mode that uses two stainless steel calibration spheres. In general, the standard calibration mode was used. The sample volume, V_s, was determined by measuring the pressure change of helium (99.9990% ultra high purity) in a calibrated volume [14]. True density, ρ_{True}, is automatically derived from V_s and its sample weight, m_s. Air, argon, hydrogen, nitrogen, and helium gases are used in gas pycnometry [17]. Helium gas of sufficient purity is the common gas choice [38] that permits one to determine the true solid sample volume since it is inert (low reactivity and non-adsorbing gas), has a low atomic radius (lowest of noble gases) and only translational degrees of freedom. Helium can be considered an ideal gas at room temperature and low pressure [17]. Hence, helium is able to penetrate and/or diffuse into the smallest pores, cracks, and crevices [14].

The filling level of the sample chamber was typically above 75%. To examine the impact of sample volume on density the samples